

REMARKS/ARGUMENTS

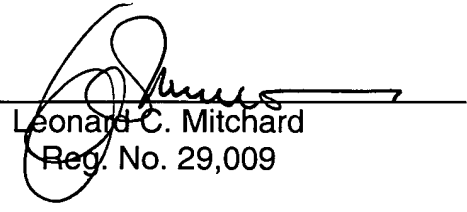
The above amendments are to insert a cross-reference to the PCT application upon which this National Phase application is based, and to revise the claims from the originally published format to correct/remove multiple dependencies. In addition, the Abstract is presented on a separate sheet attached to this amendment.

Applicants await an early action on the merits. If the Examiner finds this case is not now in condition for allowance and believes that an interview prior to first action would be helpful in focussing and/or resolving issues, applicants request the Examiner to contact their representative at the telephone number listed below to arrange a telephonic or personal interview.

Respectfully submitted,

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ABSTRACT OF THE DISCLOSURE

A method of selecting one or more 1,2,4-benzotriazine-1,4-dioxides capable of in vivo hypoxia selective cytotoxicity, wherein said 1,2,4-benzotriazine-1,4-dioxide is selected if it is determined to have each of the following characteristics (a) a solubility greater than or about 2mM in culture medium; and (b) an HT29 anoxic IC_{50} for a 4hr exposure to the 1,2,4-benzotriazine-1,4-dioxide of less than or about 40 μ M; and (c) a hypoxic cytotoxicity ratio (HCR) greater than about 20 for the HT29 cell line; and (d) a penetration half distance (PHD) greater than or about 27 μ m, and (e) the area under the plasma concentration time curve for free 1,2,4-benzotriazine-1,4-dioxide (unbound to plasma proteins), AUC_t , is greater than about 2 times the HT29 anoxic $IC_{50} \times t$ where $IC_{50} \times t$ is the product of concentration \times exposure time for 50% inhibition of cell proliferation and wherein for said 1,2,4-benzotriazine-1,4-dioxide at least one of the characteristics (a) to (e) exceeds the activity of the equivalent characteristic of Tirapazamine.